FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Mariana Coutinho Malheiros Ferreira

Respiratory morbidity in very preterm and very low birth weight infants - the first two years of life

março, 2014

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Mariana Coutinho Malheiros Ferreira

Respiratory morbidity in very preterm and very low birth weight infants - the first two years of life

Mestrado Integrado em Medicina

Área: Neonatologia

Trabalho efetuado sob a Orientação de:
Doutora Maria Hercília Ferreira Guimarães Pereira Areias

Trabalho organizado de acordo com as normas da revista:
Revista Portuguesa de Pneumologia

março, 2014

FMUP

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Mariana Coutinho Malheiros Ferreira, abaixo assinado, nº mecanográfico 200805630, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação:

Mariana Coutinho Malheiros Ferreira

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Mariana Coutinho Malheiros Ferreira

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
13735085	mimed08157@med.up.pt	916221762

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
200805630	20/03/2014

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neonatologia

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Respiratory morbidity in very preterm and very low birth weight infants – the first two years of life

ORIENTADOR

Professora Doutora Maria Hercília Ferreira Guimarães Pereira Areias

COORIENTADOR (se aplicável)

É autorizada a reprodução integral desta Dissertação/~~Monografia~~ (riscar o que não interessa) para efeitos de investigação e de divulgação pedagógica, em programas e projectos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação: Mariana Coutinho Malheiros Ferreira

Respiratory morbidity in very preterm and very low birth weight infants – the first two years of life

Mariana Ferreira, medical student[1]; Manuel Ferreira de Magalhães, MD[1,2]; Gustavo Rocha, MD[2]; Hercília Guimarães, MD, PhD[1,2]

[1] Faculty of Medicine of the University of Porto. Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

[2] Pediatrics Department. Centro Hospitalar de São João. Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

[3] Neonatology Department, Centro Hospitalar de São João. Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

Corresponding author: Mariana Ferreira (mimed08157@med.up.pt)

Abstract

Respiratory morbidity with recurrent respiratory symptoms, chronic inhaled medication use and frequent hospital admissions in the first two years of life is a common problem in very preterm and very low birth weight infants. We conducted a retrospective cohort study aiming to describe the respiratory morbidity at two years of corrected age of very preterm and very low birth weight infants and to identify potential risk factors for its development in a Portuguese-based population born in the modern neonatal care era. A total 59 children were studied. Thirteen (22.0%) had recurrent respiratory symptoms and 20.3% were using chronic respiratory medication. Health care utilization for respiratory causes was frequent (57.6%), particularly emergency department attendance (50.8%). Twenty-seven (45.8%) had additional outpatient visits for respiratory causes and hospital admission was necessary for 8 (13.6%) patients. Factors associated with increased recurrent respiratory symptoms included maternal hypertensive disorders during pregnancy, umbilical artery flow disturbances, being small for gestational age, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage and a weight percentile below 3 at 6, 12 and 24 months of corrected age. Premature rupture of membranes was negatively associated with respiratory morbidity. We conclude that respiratory morbidity is a common problem in our population and a frequent cause of health care utilization. If confirmed in larger studies, the risk factors found in our study, particularly those related to growth and weight gain during infancy, could significantly impact the care and future health of these children.

Keywords: preterm infants, very low birth weight, small for gestational age, pregnancy induced hypertension, bronchopulmonary dysplasia, retinopathy of prematurity, neonatal intensive care, respiratory tract infections, wheezing

Introduction

Preterm birth has increased over the last 20 years and survival rates have improved.[1-7] Chronic respiratory problems remain a common complication of prematurity, and very preterm[2,3,6,7] and very low birth weight (VLBW)[6,8,9] infants are especially vulnerable.

These children often experience recurrent respiratory symptoms, with wheezing being the most frequently described outcome.[6,8-11] Recurrent cough is also common, as is the need for bronchodilators and inhaled corticosteroids.[2 6,8,10,11] Rates of hospitalization are considerably higher in this population, with respiratory illnesses being the most common cause of admission.[1-4,6-8,12-15]

Several perinatal[2,3,10,13,16-18], neonatal[2,4,7,9,11,13,15,19-21] and familial factors[10,19,21-23], as well as early life exposures[2,6,9,10,13,21,22] have also been associated with increased respiratory morbidity in the first years of life.

Hospitalization rates usually decline after the second year of life and by school age symptoms typically become mild.[1-3,6,7] However, in some individuals recurrent wheezing and pulmonary function impairment may persist throughout childhood and early adulthood.[2,6,24-27]

The aim of this study is to describe respiratory morbidity at 2 years of corrected age for very preterm and VLBW infants and to identify potential risk factors for its development in a Portuguese-based population born in the modern neonatal care era.

Patients and Methods

All children born at Centro Hospitalar de São João between January 1, 2009 and December 31, 2011 with less than 32 weeks of gestational age or less than 1500 g at birth and treated at the local neonatal intensive care unit (NICU) were included. Exclusion criteria were major malformations, chromosomal disorders, congenital TORCH infection, death during NICU stay and transfer to another hospital before completing 7 days at the local NICU.

All information was collected retrospectively. Patients' clinical files were consulted and data about demographics, perinatal and neonatal characteristics was recorded (Appendix I).

Gestational age was defined by menstrual age (women with regular menstrual cycles), ultrasound examination (in the absence of a menstrual date or when a difference of two or more weeks existed between menstrual age and that derived sonographically), or the New Ballard Score (in the absence of obstetrical indexes).[28,29] Small for gestational age (SGA) was defined as a birth weight below the 10th centile of Fenton's fetal growth charts.[30]

Histological chorioamnionitis was classified according to Blanc[31] (stage I: intervilositis; stage II: chorionitis; stage III: chorioamnionitis; funisitis: polymorphonuclear leukocytes in the Wharton´s jelly or umbilical vessel walls; vasculitis: polymorphonuclear leukocytes in chorionic or umbilical blood vessel walls).

Diagnosis of respiratory distress syndrome (RDS) was made using the Vermont Oxford Network criteria: (1) PaO_2 < 50 mmHg in room air, central cyanosis in room air, a requirement for supplemental oxygen to maintain PaO_2 > 50 mmHg or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85% within the first 24 h of life and (2) a chest radiograph consistent with RDS

(reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 h of life. RDS was classified as light, moderate or severe according to X-ray appearance ranging from a light reticulogranular pattern with air bronchograms to white lungs, an adaptation from the classification by Couchard *et al.*[32]

Bronchopulmonary dysplasia (BPD) was defined according to the National Institute of Child Health and Human Development consensus criteria.[33,34] Patent ductus arteriosus (PDA) was considered when a hemodynamically significant defect was diagnosed on echocardiography. Diagnosis and staging of necrotizing enterocolitis (NEC) was made using the modified Bell criteria.[35] Retinopathy of prematurity (ROP) was staged according to the International Classification.[36] Proven neonatal sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture.

Intraventricular hemorrhage (IVH) was classified according to Papile *et al*[37] (grade I: germinal matrix hemorrhage; grade II: IVH without ventricular dilation; grade III: IVH with ventricular dilation; grade IV: germinal matrix hemorrhage or IVH with parenchymal involvement).

Afterwards, information about respiratory morbidity, care and evolution during the first two years of life (Appendix II) was collected in a single interview with the patients' parents conducted at a routine hospital visit for the child or telephonically for those who had no scheduled visits or missed their appointments

Weight percentiles at 6, 12 and 24 months of corrected age were defined according to the World Health Organization Child Growth Standards.[38]

Socioeconomical status was graded using Graffar's classification as adapted to the Portuguese population.[39]

Written or oral consent was obtained after the parents were fully informed about the study's design and purpose.

This study was approved by the Centro Hospitalar de São João's ethics committee.

Statistical analysis was performed using SPSS 19 (IBM, New York, USA). Categorical variables were described using absolute and relative frequencies and continuous variables (with non-symetrical distribution) as median and range. We used chi-square test to explore associations for categorical variables and Mann-Whitney test for continuous variables. Results are presented as odds ratio (OR) and 95% confidence intervals (95%CI). A p-value < 0.05 was considered significant.

Results

A total 119 patients met the inclusion criteria. Thirteen were excluded for malformations, 5 for chromosomal disorders, 13 for death during NICU stay and 16 for transfer to another hospital before completing 7 days at the local NICU. Additionally, 12 children were excluded for loss of follow-up and 1 for parents' refusal to participate. A total 59 children were studied.

The populations' demographics, perinatal and neonatal data are summarized in Table 1. Table 2 describes the participants' care and evolution after discharge, social and familiar characteristics.

In the first two years of life, 13 (22.0%) had recurrent respiratory symptoms and 12 (20.3%) were using chronic respiratory medication. Health care utilization for respiratory causes was frequent (57.6%), particularly emergency department attendance (50.8%). Hospital admission was necessary for 8 (13.6%) patients. Twenty-seven (45.8%) had additional outpatient visits for respiratory causes. Eighteen (30.5%) parents had to miss at least one day at work for their child's respiratory problems (Table 3).

Being SGA was significantly associated with the presence of recurrent respiratory symptoms (OR 3.84, 95% CI 1.02-14.37), as were maternal hypertensive disorders during pregnancy (OR 4.17, 95% CI 1.02-17.05) and umbilical artery flow disturbances (OR 10.67, 95% CI 2.61-43.64). Premature rupture of membranes (PROM) was negatively associated with the presence of respiratory symptoms in the first two years of life (Table 4).

BPD (OR 9.78, 95% CI 1.55-61.73), ROP (stage ≥ II) (OR 5.00, 95% CI 1.03-24.30) and IVH (grade ≥ III) had significant positive associations with respiratory morbidity, as did a weight percentile below 3 at 6, 12 and 24 months of corrected age (Table 4).

We found no significant associations for gestational age, birth weight, SNAPPE-II and CRIB scores, maximal fraction of inspired O_2 during NICU stay, duration of NICU stay, duration of breastfeeding, number of people in the household and age at beginning of daycare attendance (data not shown).

Discussion

The prevalence of respiratory symptoms and chronic respiratory medication use in our population is lower than that described in most studies.[6,11,12,18,40,41] The great variability in inclusion and exclusion criteria, definition of outcomes and age at evaluation among studies makes it difficult to compare results. Still, the fact that our population is highly selected, excluding outborn patients with potentially more severe neonatal disease justifying their transfer to a tertiary center, could explain some of the differences observed. Also, the low prevalence of BPD in our population (10.2%), although comparable to a previous Portuguese study (12.9%)[42], could contribute to the overall low respiratory morbidity. However, rates described for preterm children without BPD are still higher than those we found.[11,41] Differences in prescription criteria could explain some variations in medication use as well.

The rate of hospital admissions for respiratory causes was also lower than that found in previous studies, although similar rates have been described.[2,11,40,41,43] Once again, differences in inclusion and exclusion criteria, age at evaluation and admission criteria make any conclusive comparisons difficult.

We found a significant association between being SGA and recurrent respiratory symptoms. While some have found a significant association between intrauterine growth restriction (IUGR) and persistent wheezing, others failed to confirm it.[19,44] Still, our results are supported by animal studies showing an association between IUGR and persisting alterations in lung structure and function and by findings of abnormal lung function in school aged children born SGA.[45,46]

While no studies have described an association between umbilical artery flow disturbances and respiratory morbidity during infancy, we believe our results to be consistent with those by Hartung *et al*[47] describing a positive association between

absent or reversed end-diastolic umbilical artery flow and BPD. Also, our findings of a positive association between hypertensive disorders of pregnancy and recurrent respiratory symptoms are in line with those by Rusconi *et al.*[48]

It is possible that IUGR, hypertensive disorders of pregnancy and umbilical artery flow abnormalities represent to some extent a common pathway of placental insufficiency and altered angiogenesis, as proposed by others.[49, 50] However, more studies are necessary to confirm this.

We found a negative association between PROM and recurrent symptoms. Teune *et al*[16] found the opposite and Williams *et al*[51] described an increased incidence of hospital admissions for respiratory causes in these infants. However, PROM has been associated with a reduced risk of RDS. The proposed biological mechanism behind this association states PROM as an inflammation inducer that accelerates lung maturity.[2, 52] Therefore, although lacking support from epidemiological studies, we believe our findings to be biologically plausible as infants with PROM may present with less RDS and need less aggressive respiratory interventions, and therefore develop less respiratory morbidity.

Cesarean section has been associated with the development of asthma and recurrent wheezing.[53,54] The lack of exposure to vaginal flora could alter immune system development in these children, with a subsequent increased risk for asthma and atopy.[53,54] Because we studied a very young population, we didn't include asthma diagnosis as a respiratory outcome; follow-up of this population is crucial to clarify whether those with recurrent respiratory symptoms during infancy are diagnosed with asthma in the future.[54,55]

Our findings of a positive association between BPD and respiratory morbidity during infancy are in line with what has been described.[4,7,11,19,21]

ROP and IVH were also significantly associated with recurrent respiratory symptoms. We found no studies describing a relation between these disorders and respiratory morbidity in the first years of life. However, they appear to share common risk factors and an association between ROP and BPD has been described.[42,56-58] Also, because we didn't exclude children with neurological disorders, it is possible that infants with ROP and particularly IVH represent those with the worst neurological outcome, which may account for their increased respiratory morbidity.[59-61]

Having a weight percentile below 3 at 6, 12 or 24 months was significantly associated with respiratory morbidity. Most studies have described the negative effects of rapid weight gain or being overweight on pulmonary function and the development of asthma and recurrent wheezing.[62-64] However, these findings are not universal[65] and a study by Zhang *et al*[66] found that being overweight during the first two years of life was associated with a decreased risk of asthma and better lung function. Proposed explanations emphasized the influence of a well-nourished state in promoting maximal postnatal lung development at an age when great alveolar development and multiplication occurs.[66] Because we chose to focus on the effects of poor weight evolution and underweight persistence, the extent to which our results may be compared to previous reports is limited.

The small number of participants is one of our study's limitations and may justify the lack of significant associations between respiratory morbidity and several of the factors we tested for. We chose to define outcomes as reported by parents, a method frequently used in other studies[4]; however, it creates the potential for information bias. Also, the study's retrospective design creates the possibility of recall bias. Future studies with larger samples are needed to clarify the significance of our findings. The creation of predictive models for respiratory morbidity in the first years

but also later in life would be an interesting goal, allowing a more accurate identification of children who might benefit from closer follow-up and specific preventive measures, and therefore promoting better allocation of health resources.

References

1. Doyle LW. Chapter 11 - Long-Term Pulmonary Outcome of Preterm Infants. In: Bancalari E, editor. The Newborn Lung: Neonatology Questions and Controversies (Second Edition). Philadelphia: W.B. Saunders; 2012: 235-43.

2. Kwinta P, Pietrzyk JJ. Preterm birth and respiratory disease in later life. Expert Rev Respir Med. 2010 Oct;4(5):593-604.

3. Greenough A. Long-term respiratory consequences of premature birth at less than 32 weeks of gestation. Early Hum Dev. 2013 Oct;89 Suppl 2:S25-7.

4. de Mello RR, Dutra MV, Lopes JM. [Respiratory morbidity in the first year of life of preterm infants discharged from a neonatal intensive care unit]. J Pediatr (Rio J). 2004 Nov-Dec;80(6):503-10.

5. Stoelhorst GM, Rijken M, Martens SE, Brand R, den Ouden AL, Wit JM, et al. Changes in neonatology: comparison of two cohorts of very preterm infants (gestational age <32 weeks): the Project On Preterm and Small for Gestational Age Infants 1983 and the Leiden Follow-Up Project on Prematurity 1996-1997. Pediatrics. 2005 Feb;115(2):396-405.

6. Elder DE, Hagan R, Evans SF, Benninger HR, French NP. Recurrent wheezing in very preterm infants. Arch Dis Child Fetal Neonatal Ed. 1996 May;74(3):F165-71.

7. Greenough A. Long term respiratory outcomes of very premature birth (<32 weeks). Semin Fetal Neonatal Med. 2012 Apr;17(2):73-6.

8. McLeod A, Ross P, Mitchell S, Tay D, Hunter L, Hall A, et al. Respiratory health in a total very low birthweight cohort and their classroom controls. Arch Dis Child. 1996 Mar;74(3):188-94.

9. Chalfun G, Mello RR, Dutra MV, Andreozzi VL, Silva KS. [Risk factors for respiratory morbidity at 12 to 36 months in very low birth weight premature infants previously admitted to a public neonatal intensive care unit]. Cad Saude Publica. 2009 Jun;25(6):1399-408.

10. Greenough A, Limb E, Marston L, Marlow N, Calvert S, Peacock J. Risk factors for respiratory morbidity in infancy after very premature birth. Arch Dis Child Fetal Neonatal Ed. 2005 Jul;90(4):F320-3.

11. Perez Perez G, Navarro Merino M, Romero Perez MM, Saenz Reguera C, Pons Tubio A, Polo Padillo J. [Respiratory morbidity after hospital discharge in premature infants born at < or = 32 weeks gestation with bronchopulmonary dysplasia]. An Pediatr (Barc). 2004 Feb;60(2):117-24.

12. Greenough A. Late respiratory outcomes after preterm birth. Early Hum Dev. 2007 Dec;83(12):785-8.

13. Resch B, Pasnocht A, Gusenleitner W, Muller W. Rehospitalisations for respiratory disease and respiratory syncytial virus infection in preterm infants of 29-36 weeks gestational age. J Infect. 2005 Jun;50(5):397-403.

14. Gunville CF, Sontag MK, Stratton KA, Ranade DJ, Abman SH, Mourani PM. Scope and impact of early and late preterm infants admitted to the PICU with respiratory illness. J Pediatr. 2010 Aug;157(2):209-14 e1.

15. de Mello RR, Dutra MV, Ramos JR, Daltro P, Boechat M, Lopes JM. Neonatal risk factors for respiratory morbidity during the first year of life among premature infants. Sao Paulo Med J. 2006 Mar 2;124(2):77-84.

16. Teune MJ, van Wassenaer AG, van Buuren S, Mol BW, Opmeer BC, Dutch PCSG. Perinatal risk-indicators for long-term respiratory morbidity among preterm or

very low birth weight neonates. Eur J Obstet Gynecol Reprod Biol. 2012 Aug;163(2):134-41.

17. Rocha G, Proença E, Quintas C, Rodrigues T, Guimarães H. Histological chorioamnionitis and lung damage in preterm newborns. Arquivos de Medicina. 2005;19:15-21.

18. Kumar R, Yu Y, Story RE, Pongracic JA, Gupta R, Pearson C, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: a prospective birth cohort study. J Allergy Clin Immunol. 2008 Apr;121(4):878-84 e6.

19. Broughton S, Thomas MR, Marston L, Calvert SA, Marlow N, Peacock JL, et al. Very prematurely born infants wheezing at follow-up: lung function and risk factors. Arch Dis Child. 2007 Sep;92(9):776-80.

20. Greenough A. Home oxygen status and rehospitalisation and primary care requirements of infants with chronic lung disease. Arch Dis Child. 2002;86(1):40-3.

21. Hagen EW, Sadek-Badawi M, Palta M. Daycare attendance and risk for respiratory morbidity among young very low birth weight children. Pediatr Pulmonol. 2009 Nov;44(11):1093-9.

22. Latzin P, Frey U, Roiha HL, Baldwin DN, Regamey N, Strippoli MP, et al. Prospectively assessed incidence, severity, and determinants of respiratory symptoms in the first year of life. Pediatr Pulmonol. 2007 Jan;42(1):41-50.

23. Belanger K, Beckett W, Triche E, Bracken MB, Holford T, Ren P, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. Am J Epidemiol. 2003 Aug 1;158(3):195-202.

24. Guimarães H, Rocha G, Pissarra S, Guedes MB, Nunes T, Vitor B. Respiratory outcomes and atopy in school-age children who were preterm at birth, with and without bronchopulmonary dysplasia. Clinics. 2011;66(3):425-30.

25. Choukroun ML, Feghali H, Vautrat S, Marquant F, Nacka F, Leroy V, et al. Pulmonary outcome and its correlates in school-aged children born with a gestational age </= 32 weeks. Respir Med. 2013 Dec;107(12):1966-76.

26. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007 Nov 8;357(19):1946-55.

27. Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. Pediatrics. 2010 Aug;126(2):342-51.

28. MacDonald H, American Academy of Pediatrics. Committee on F, Newborn. Perinatal care at the threshold of viability. Pediatrics. 2002 Nov;110(5):1024-7.

29. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991 Sep;119(3):417-23.

30. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.

31. Blanc WA. Pathology of the placenta, membranes, and umbilical cord in bacterial, fungal, and viral infections in man. Monogr Pathol. 1981 (22):67-132.

32. Couchard M, Polge J, Bomsel F. [Hyaline membrane disease: diagnosis, radiologic surveillance, treatment and complications]. Ann Radiol (Paris). 1974 Nov;17(7):669-83.

33. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001 Jun;163(7):1723-9.

34. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005 Dec;116(6):1353-60.

35. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986 Feb;33(1):179-201.

36. Classification of Retinopathy of P. The international classification of retinopathy of prematurity revisited. Archives of Ophthalmology. 2005;123(7):991-9.

37. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978 Apr;92(4):529-34.

38. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization; 2006 (312 pages).

39. Amaro F. A classificação das famílias segundo a Escala de Graffar. Lisboa: Fundação Nossa Senhora do Bom Sucesso; 2001.

40. Pramana IA, Latzin P, Schlapbach LJ, Hafen G, Kuehni CE, Nelle M, et al. Respiratory symptoms in preterm infants: burden of disease in the first year of life. Eur J Med Res. 2011 May 12;16(5):223-30.

41. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. J Pediatr. 2007 Mar;150(3):256-61.

42. Guimaraes H, Rocha G, Vasconcellos G, Proenca E, Carreira ML, Sossai Mdo R, et al. Risk factors for bronchopulmonary dysplasia in five Portuguese neonatal intensive care units. Rev Port Pneumol. 2010 May-Jun;16(3):419-30.

43. Rhein LM, Konnikova L, McGeachey A, Pruchniewski M, Smith VC. The role of pulmonary follow-up in reducing health care utilization in infants with bronchopulmonary dysplasia. Clin Pediatr (Phila). 2012 Jul;51(7):645-50.

44. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. Am J Respir Crit Care Med. 1999 Nov;160(5 Pt 1):1617-22.

45. Pike K, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. Semin Fetal Neonatal Med. 2012 Apr;17(2):92-8.

46. Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. BMJ. 1993 Mar 27;306(6881):817-20.

47. Hartung J, Kalache KD, Heyna C, Heling KS, Kuhlig M, Wauer R, et al. Outcome of 60 neonates who had ARED flow prenatally compared with a matched control group of appropriate-for-gestational age preterm neonates. Ultrasound Obstet Gynecol. 2005 Jun;25(6):566-72.

48. Rusconi F, Galassi C, Forastiere F, Bellasio M, De Sario M, Ciccone G, et al. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. Am J Respir Crit Care Med. 2007 Jan 1;175(1):16-21.

49. Hansen AR, Barnes CM, Folkman J, McElrath TF. Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. J Pediatr. 2010 Apr;156(4):532-6.

50. Wang KG, Chen CY, Chen YY. The effects of absent or reversed end-diastolic umbilical artery Doppler flow velocity. Taiwan J Obstet Gynecol. 2009 Sep;48(3):225-31.

51. Williams O, Michel B, Hutchings G, Debauche C, Hubinont C. Two-year neonatal outcome following PPROM prior to 25 weeks with a prolonged period of oligohydramnios. Early Hum Dev. 2012 Aug;88(8):657-61.

52. Sims EJ, Vermillion ST, Soper DE. Preterm premature rupture of the membranes is associated with a reduction in neonatal respiratory distress syndrome. American Journal of Obstetrics and Gynecology. 2002;187(2):268-72.

53. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy. 2008 Apr;38(4):629-33.

54. Negele K, Heinrich J, Borte M, von Berg A, Schaaf B, Lehmann I, et al. Mode of delivery and development of atopic disease during the first 2 years of life. Pediatr Allergy Immunol. 2004 Feb;15(1):48-54.

55. Magnus MC, Haberg SE, Stigum H, Nafstad P, London SJ, Vangen S, et al. Delivery by Cesarean section and early childhood respiratory symptoms and disorders: the Norwegian mother and child cohort study. Am J Epidemiol. 2011 Dec 1;174(11):1275-85.

56. Yang CY, Lien R, Yang PH, Chu SM, Hsu JF, Fu RH, et al. Analysis of incidence and risk factors of retinopathy of prematurity among very-low-birth-weight infants in North Taiwan. Pediatr Neonatol. 2011 Dec;52(6):321-6.

57. Aly H, Hammad TA, Essers J, Wung JT. Is mechanical ventilation associated with intraventricular hemorrhage in preterm infants? Brain Dev. 2012 Mar;34(3):201-5.

58. Giapros V, Drougia A, Asproudis I, Theocharis P, Andronikou S. Low gestational age and chronic lung disease are synergistic risk factors for retinopathy of prematurity. Early Hum Dev. 2011 Oct;87(10):653-7.

59. Sugimoto S, Furukawa A, Hatsukawa Y, Yanagihara K, Saito Y. Weak association between retinopathy of prematurity and neurological disorders in childhood. Jpn J Ophthalmol. 1998 Mar-Apr;42(2):142-5.

60. Sherlock RL, Anderson PJ, Doyle LW, Victorian Infant Collaborative Study G. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early Hum Dev. 2005 Nov;81(11):909-16.

61. Fitzgerald DA, Follett J, Van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. Paediatr Respir Rev. 2009 Mar;10(1):18-24.

62. Lucas JS, Inskip HM, Godfrey KM, Foreman CT, Warner JO, Gregson RK, et al. Small size at birth and greater postnatal weight gain: relationships to diminished infant lung function. Am J Respir Crit Care Med. 2004 Sep 1;170(5):534-40.

63. Turner S, Zhang G, Young S, Cox M, Goldblatt J, Landau L, et al. Associations between postnatal weight gain, change in postnatal pulmonary function, formula feeding and early asthma. Thorax. 2008 Mar;63(3):234-9.

64. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children. J Allergy Clin Immunol. 2014 Feb 11.

65. Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, et al. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. J Allergy Clin Immunol. 2009 Jun;123(6):1312-8 e2.

66. Zhang Z, Lai HJ, Roberg KA, Gangnon RE, Evans MD, Anderson EL, et al. Early childhood weight status in relation to asthma development in high-risk children. J Allergy Clin Immunol. 2010 Dec;126(6):1157-62.

Tables and Figures

Table 1– Demographics, perinatal and neonatal characteristics of the study population

	Total (n=59)	
Demographics		
Female, n (%)	36	(61.0)
Gestational age (weeks), median (range)	30	(25-37)
Birth weight (g), median (range)	1195	(520 – 2435)
Small for gestational age (SGA), n (%)	26	(44.1)
Assymetrical SGA, n (%)	7	(11.9)
Gestation		
Multiple gestation, n (%)	21	(35.6)
Prenatal corticosteroids, n (%)	54	(91.5)
Incomplete cycle, n (%)	9	(15.3)
Complete cycle, n (%)	45	(76.3)
Smoking during pregnancy, n (%)	9	(15.3)
Gestational diabetes, n (%)	5	(8.5)
Chronic maternal hypertension, n (%)	3	(5.1)
Hypertensive disorders of pregnancy, n (%)	11	(18.6)
Pre-eclampsia, n (%)	9	(15.3)
Eclampsia, n (%)	1	(1.7)
HELLP syndrome, n (%)	2	(3.4)
Histological chorioamnionitis, n (%)	19	(32.2)
Funisitis and/or chorionic vasculitis, n (%)	10	(16.9)

Clinical chorioamnionitis, n (%)	2	(3.4)
Placental abruption, n (%)	3	(5.1)
Umbilical artery flow disturbances*, n (%)	14	(23.7)
Delivery		
Caesarian section, n (%)	49	(83.1)
Premature rupture of membranes, n (%)	10	(16.9)
Hours of membrane rupture, median (range)	62	(3-1992)
Intrapartum antibiotics for premature rupture of membranes, n (%)	6	(10.2)
APGAR (1st minute)		
0-3, n (%)	6	(10.2)
4-6, n (%)	15	(25.4)
7-10, n (%)	38	(64.4)
APGAR (5th minute)**		
0-3, n (%)	1	(1.7)
4-6, n (%)	6	(10.3)
7-10, n (%)	51	(87.9)
Need for resuscitation, n (%)	30	(50.8)
Early CPAP, n (%)	27	(45.8)
Neonatal period (NICU stay)		
SNAPPE-II score***		
0-9, n (%)	32	(54.2)
10-19, n (%)	6	(10.2)
20-29, n (%)	8	(13.6)
30-39, n (%)	3	(5.1)

40-49, n (%)	2	(3.4)
50-59, n (%)	1	(1.7)
60-69, n (%)	1	(1.7)
70-79, n (%)	0	(0.0)
≥ 80, n (%)	0	(0.0)
CRIB score***		
0-5, n (%)	47	(79.7)
6-10, n (%)	6	(10.2)
11-15, n (%)	0	(0.0)
≥ 16, n (%)	0	(0.0)
RDS, n (%)	29	(49.2)
Mild, n (%)	13	(22.0)
Moderate, n (%)	11	(18.6)
Severe, n (%)	5	(8.5)
Surfactant administration, n (%)	29	(49.2)
Conventional mechanical ventilation, n (%)	27	(45.8)
Invasive ventilation only, n (%)	1	(1.7)
Invasive ventilation and nCPAP, n (%)	26	(44.1)
nCPAP only, n (%)	24	(40.7)
Days of conventional mechanical ventilation, median (range)	7	(1-59)
Days of nCPAP, median (range)	27	(2-62)
Supplemental oxygen, n (%)	29	(49.2)
Maximal fraction of inspired O_2, median (range)	0.21	(0.21-1.00)
Days of supplemental oxygen, median (range)	7	(1-121)

Supplemental oxygen on discharge, n (%)	1	(1.7)
Bronchopulmonary dysplasia, n (%)	6	(10.2)
Mild, n (%)	2	(3.4)
Moderate, n (%)	1	(1.7)
Severe, n (%)	3	(5.1)
Patent ductus arteriosus, n (%)	14	(23.7)
Necrotizing enterocolitis (≥2A), n (%)	3	(5.1)
Retinopathy of prematurity (≥II), n (%)	8	(13.6)
Intraventricular hemorrhage (≥ III), n (%)	3	(3.4)
Hidrocephalus, n (%)	2	(3.4)
Periventricular cystic leukomalacia, n (%)	6	(15.3)
Sepsis, n (%)	23	(39.0)
Days at the UCIN, median (range)	43	(7-154)
Weight on discharge (g), median (range)	1920	(848-2800)
Weight percentile on discharge		
< 3, n (%)	43	(72.9)
≥ 3, n (%)	16	(27.1)
Season of discharge		
Spring, n (%)	22	(37.3)
Summer, n (%)	14	(23.7)
Autumn, n (%)	8	(13.6)
Winter, n (%)	15	(25.4)

* Includes umbilical artery flow absence or inversion ;**n=58; ***n=53.

Table 2 – Care and evolution after discharge from NICU

	Total (n=59)	
Breastfeeding, n (%)	34	(57.6)
Duration of breastfeeding (months), median (range)	3	(1-27)
Isolation during first winter season, n (%)	17	(28.8)
Other preventive measures, n (%)	35	(59.3)
Antipneumococcal vaccine, n (%)	57	(96.6)
Palivizumab, n (%)	47	(79.7)
Influenza vaccine, n (%)	20	(33.9)
Weight percentile at 6 months of corrected age, n (%)		
< 3, n (%)	12	(20.7)
≥ 3, n (%)	46	(79.3)
Weight percentile at 12 months of corrected age, n (%)		
< 3, n (%)	9	(16.1)
≥ 3, n (%)	47	(83.9)
Weight percentile at 24 months of corrected age, n (%)		
< 3, n (%)	5	(8.8)
≥ 3, n (%)	52	(91.2)
Social and familiar characteristics		
Socioeconomical status (Graffar classification)		
Class I, n (%)	17	(28.8)
Class II, n (%)	20	(33.9)
Class III, n (%)	18	(30.5)
Class IV, n (%)	4	(6.8)
Class V, n (%)	0	(0.0)

Number of people in the household, median (range)	4	(2-7)
Preschool aged siblings, n (%)	24	(40.7)
Stayed at home during the first two years of life, n (%)	44	(74.6)
Day care attendance, n (%)	15	(25.4)
Age at beginning of day care attendance, median (range)	9	(0-20)
Any smokers in the household, n (%)	27	(45.8)
Fireplace in the household, n (%)	26	(44.1)
Family history of asthma, n (%)	24	(40.7)
Maternal, n (%)	13	(22.0)
Family history of atopy, n (%)	22	(37.3)
Maternal, n (%)	12	(20.3)

* (n= 58); ** (n=56); ***(n=57)

Table 3 – Respiratory morbidity in the first two years of life

	Total (n=59)
Symptoms	
Recurrent respiratory symptoms, n (%)	13 (22.0)
Recurrent cough, n (%)	4 (6.8)
Recurrent wheeze, n (%)	3 (5.1)
Recurrent respiratory symptoms on exertion, n (%)	10 (16.9)
Waking with cough, n (%)	4 (6.8)
Waking with wheeze, n (%)	3 (5.1)
Waking with dyspnea, n (%)	4 (6.8)
Respiratory symptoms with respiratory illness only, n (%)	30 (50.8)
Cough, n (%)	33 (55.9)
Wheeze, n (%)	28 (47.5)
Need for respiratory medication	
Chronic respiratory medication*, n (%)	12 (20.3)
Long acting β agonists, n (%)	0 (0.0)
Daily inhaled corticosteroids, n (%)	5 (8.5)
Daily short acting β agonists, n (%)	2 (3.4)
Frequent inhaled antimuscarinics use, n (%)	2 (3.4)
Daily leukotriene antagonists use, n (%)	2 (3.4)
Frequent antihistamines use, n (%)	5 (8.5)
Respiratory medication for respiratory illness only**, n (%)	25 (42.4)

Health care utilization	
Health care utilization for respiratory causes, n (%)	34 (57.6)
Additional outpatient visits for respiratory causes, n (%)	27 (45.8)
Emergency department attendance for respiratory causes, n (%)	30 (50.8)
Emergency department attendance for bronchiolitis, n (%)	16 (27.1)
Emergency department attendance for pneumonia, n (%)	2 (3.4)
Emergency department attendance for other respiratory causes, n (%)	17 (28.8)
Hospital admission for respiratory causes, n (%)	8 (13.6)
Hospital admission for bronchiolitis, n (%)	7 (11.9)
Hospital admission for pneumonia, n (%)	1 (1.7)
Hospital admission for other respiratory causes, n (%)	3 (5.1)
Impact on parents' life	
Any missed days at work, n (%)	18 (30.5)
Number of days missed at work by parents, median (range)	7 (2-10)

*Includes inhaled long and short acting β agonists, inhaled antimuscarinics, inhaled corticosteroids, oral leukotriene antagonists and oral antihistamines; **Includes inhaled long and short acting β agonists, inhaled antimuscarinics, inhaled corticosteroids, and oral antihistamines.

Table 4 – Factors associated with respiratory morbidity in the first two years of life

	Recurrent respiratory symptoms, n (%)	**OR (95%CI)**	**p**
Overall	13 (22.0)		
Sex			
Female	9 (25.0)	1.00 (ref)	
Male	4 (17.4)	0.63 (0.17-2.36)	0.49
Small for gestational age (SGA)			
No	4 (12.1)	1.00 (ref)	
Yes	9 (34.6)	**3.84 (1.02-14.37)**	**0.04**
Assymetrical SGA			
No	12 (23.1)	1.00 (ref)	
Yes	1 (14.3)	0.56 (0.06-5.08)	0.58
Prenatal corticosteroids			
No	0 (0.0)	1.00 (ref)	
1 dose	3 (33.3)	n.a.	
2 doses	10 (22.2)	n.a.	0.21
Smoking during pregnancy			
No	12 (24.0)	1.00 (ref)	
Yes	1 (11.1)	0.40 (0.05-3.49)	0.36
Gestational diabetes			
No	13 (24.1)	1.00 (ref)	
Yes	0 (0.0)	n.a.	0.11
			0.06

Chronic maternal hypertension			
No	11 (19.6)	1.00 (ref)	
Yes	2 (66.7)	8.18 (0.68-98.62)	
Hypertensive disorders of pregnancy			
No	8 (16.7)	1.00 (ref)	
Yes	5 (45.5)	**4.17 (1.02-17.05)**	**0.04**
Placental disorders*			
No	9 (23.1)	1.00 (ref)	
Yes	4 (20.0)	0.83 (0.22-3.14)	0.79
Umbilical artery flow disturbances**			
No	5 (11.1)	1.00 (ref)	
Yes	8 (57.1)	**10.67 (2.61-43.64)**	**0.001**
Caesarian section			
No	0 (0.0)	1.00 (ref)	
Yes	13 (26.5)	n.a.	**0.02**
Premature rupture of membranes			
No	13 (26.5)	1.00 (ref)	
Yes	0 (0.0)	n.a.	**0.02**
APGAR (5th minute)			
0-6	2 (28.6)	1.00 (ref)	
≥7	11 (21.6)	0.69 (0.12-4.04)	0.68
			0.38

Need for resuscitation			
No	5 (17.2)	1.00 (ref)	
Yes	8 (26.7)	1.75 (0.50-6.14)	
Early CPAP			
No	10 (31.3)	1.00 (ref)	
Yes	3 (11.1)	0.28 (0.70-1.13)	0.06
RDS			
No	8 (26.7)	1.00 (ref)	
Yes	5 (17.2)	0.57 (0.16-2.02)	0.38
Surfactant administration			
No	7 (23.3)	1.00 (ref)	
Yes	6 (20.7)	0.86 (0.25-2.95)	0.81
Conventional mechanical ventilation			
No	7 (21.9)	1.00 (ref)	
Yes	6 (22.2)	1.02 (0.30-3.51)	0.97
nCPAP only			
No	10 (28.6)	1.00 (ref)	
Yes	3 (12.5)	0.36 (0.09-1.47)	0.13
Supplemental oxygen			
No	6 (20.0)	1.00 (ref)	
Yes	7 (24.1)	1.27 (0.37-4.37)	0.70
Bronchopulmonary dysplasia			
No	9 (17.0)	1.00 (ref)	
Yes	4 (66.7)	**9.78 (1.55-61.73)**	**0.01**

Patent ductus arteriosus			
No	10 (22.2)	1.00 (ref)	
Yes	3 (21.4)	0.96 (0.22-4.10)	0.95
Necrotizing enterocolitis (≥2A)			
No	12 (21.4)	1.00 (ref)	
Yes	1 (33.3)	1.83 (0.15-21.98)	0.64
Retinopathy of prematurity (≥II)			
No	8 (16.7)	1.00 (ref)	
Yes	4 (50.0)	5.00 (1.03-24.30)	**0.05**
Intraventricular hemorrhage (≥ III)			
No	11 (19.3)	1.00 (ref)	
Yes	2 (100.0)	n.a.	**0.01**
Hidrocephalus			
No	12 (21.1)	1.00 (ref)	
Yes	1 (50.0)	3.75 (0.22-64.44)	0.38
Periventricular cystic leukomalacia			
No	12 (24.0)	1.00 (ref)	
Yes	1 (11.1)	0.40 (0.05-3.49)	0.36
Sepsis			
No	6 (16.7)	1.00 (ref)	
Yes	7 (30.4)	2.19 (0.63-7.62)	0.22
Weight percentile on discharge			
< 3	10 (23.3)	1.00 (ref)	
≥ 3	3 (18.8)	0.76 (0.18-3.22)	0.71
			0.90

Season of discharge			
Spring	4 (18.2)	1.00 (ref)	
Summer	4 (28.6)	1.80 (0.37-8.80)	
Autumn	2 (25.0)	1.50 (0.22-10.36)	
Winter	3 (20.0)	1.13 (0.21-5.95)	
Breastfeeding			
No	7 (28.0)	1.00 (ref)	
Yes	6 (17.6)	0.55 (0.16-1.91)	0.35
Isolation during first winter season			
No	10 (23.8)	1.00 (ref)	
Yes	3 (17.6)	0.67 (0.16-2.88)	0.60
Antipneumococcal vaccine			
No***	2 (40.0)	1.00 (ref)	
Yes	11 (20.4)	0.38 (0.06-2.59)	0.34
Palivizumab			
No	4 (33.3)	1.00 (ref)	
Yes	9 (19.1)	0.47 (0.12-1.93)	0.31
Influenza vaccine			
No	8 (18.6)	1.00 (ref)	
Yes	5 (31.3)	1.99 (0.54-7.35)	0.31
Weight percentile at 6 months of corrected age			
< 3	7 (58.3)	1.00 (ref)	
≥ 3	6 (13.0)	0.11 (0.03-0.45)	**0.002**
			0.001

Weight percentile at 12 months of corrected age			
< 3	6 (66.7)	1.00 (ref)	
≥ 3	6 (12.8)	0.07 (0.01-0.37)	
Weight percentile at 24 months of corrected age			
< 3	4 (80.0)	1.00 (ref)	
≥ 3	9 (17.3)	0.05 (0.01-0.53)	**0.004**
Socioeconomical status (Graffar classification)			
Class I	4 (23.5)	1.00 (ref)	
Class II	2 (10.0)	0.36 (0.06-2.28)	
Class III	6 (33.3)	1.63 (0.37-7.20)	
Class IV	1 (25.0)	1.08 (0.09-13.54)	0.35
Preschool aged siblings			
No	10 (28.6)	1.00 (ref)	
Yes	3 (12.5)	0.36 (0.09-1.47)	0.13
Day care attendance			
No	11 (25.0)	1.00 (ref)	
Yes	2 (13.3)	0.46 (0.09-2.37)	0.33
Any smokers in the household			
No	7 (21.9)	1.00 (ref)	
Yes	6 (22.2)	1.02 (0.30-3.51)	0.97
			0.27

Fireplace in the household			
No	9 (27.3)	1.00 (ref)	
Yes	4 (15.4)	0.49 (0.13-1.80)	
Family history of asthma			
No	8 (22.9)	1.00 (ref)	
Yes	5 (20.8)	0.89 (0.25-3.14)	0.85
Family history of atopy			
No	6 (16.2)	1.00 (ref)	
Yes	7 (31.8)	2.41 (0.69-8.44)	0.17

*Includes histological chorioamnionitis, funisitis and chorionic vasculitis;** Includes umbilical artery flow absence or inversion; *** Incomplete immunization (1 or 2 doses) or no immunization.

Appendices

APPENDIX I – Questionnaire about demographic, perinatal and neonatal data

RESPIRATORY MORBIDITY IN VERY PRETERM AND VERY LOW BIRTH WEIGHT INFANTS – THE FIRST TWO YEARS OF LIFE

ID: _____

DEMOGRAPHICS

Birth date ___ / ___ / _____

Sex F(0)☐ M(1)☐

Gestational age _____ days

Birth weight _____ g

Small for gestational age (SGA) no (0)☐ yes (1)☐

Assymetrical SGA no (0)☐ yes (1)☐

GESTATION

Multiple gestation no (0)☐ yes (1)☐

Prenatal corticosteroids no (0)☐ incomplete cycle (one betamethasone administration)(1)☐
Complete cycle (two betamethasone administrations) (2)☐

Smoking during pregnancy no(0)☐ yes(1)☐

Gestational diabetes no(0)☐ yes(1)☐

Chronic maternal hypertension no(0)☐ yes(1)☐

Pre-eclampsia no(0)☐ yes(1)☐

Eclampsia no(0)☐ yes(1)☐

HELLP syndrome no(0)☐ yes(1)☐

Placental histology:

Histological chorioamnionitis no(0)☐ stage I (1)☐ stage II (2)☐ stage III (3)☐

Funisitis no$_{(0)}$☐ yes$_{(1)}$☐

Chorionic vasculitis no$_{(0)}$☐ yes$_{(1)}$☐

Clinical chorioamnionitis no$_{(0)}$☐ yes$_{(1)}$☐

Placental abruption no$_{(0)}$☐ yes$_{(1)}$☐

Umbilical artery flow disturbances (absence, inversion) no$_{(0)}$☐ yes$_{(1)}$☐

DELIVERY

Type of delivery eutocic $_{(0)}$☐ cesarean section $_{(1)}$☐

Premature ruprture of membranes no$_{(0)}$☐ yes$_{(1)}$☐

Intrapartum antibiotics no$_{(0)}$☐ yes$_{(1)}$☐ Justification:_____

APGAR (1st and 5th minutes) ____ / ____ / ____

Ressuscitation: no$_{(0)}$☐ yes$_{(1)}$☐

NEONATAL PERIOD

SNAPPE-II _____ CRIB _____

Respiratory distress syndrome no $_{(0)}$☐ light $_{(1)}$☐ moderate $_{(2)}$☐ severe $_{(3)}$☐

Surfactant administration no $_{(0)}$☐ yes$_{(1)}$☐

Conventional mechanical ventilation (>12h) no$_{(0)}$☐ yes$_{(1)}$☐ Duration: _____days

nCPAP (>12h) no$_{(0)}$☐ yes$_{(1)}$☐ Duration: _____days

Higher FiO_2 (>24h): _____

Duration of oxygen supplementation: _____ days

Bronchopulmonary dysplasia no $_{(0)}$☐ light$_{(1)}$☐ moderate$_{(2)}$☐ severe$_{(3)}$☐

Persistent ductus arteriosus no$_{(0)}$☐ yes$_{(1)}$☐

Necrotizing enterocolitis (grade ≥ 2A Bell) no(0)☐ yes(1)☐

Retinopathy of prematurity (higher stage) no(0)☐ stage I (1)☐ stage II (2)☐ stage III (3)☐
grau IV (4)☐ grau V (5)☐

Intraventricularvhemorrhage no (0)☐ stage I (1)☐ stage II (2)☐ stage III (3)☐ stage IV (4)☐

Hidrocephalus (with ventriculoperitoneal derivation) no(0)☐ yes(1)☐

Periventricular leukomalacia no(0)☐ yes(1)☐

Sepsis no(0)☐ yes(1)☐

Days at NICU: _____

Weight on discharge: _____ g;

Weight percentile on discharge (Fenton curves): <3 (0)☐ ≥ 3 (1)☐

Season of NICU discharge: Spring (0)☐ Summer (1)☐ Autumn (2)☐ Winter (3)☐

APPENDIX II – Questionnaire about social and familiar data and follow-up in the first two years of life

RESPIRATORY MORBIDITY IN VERY PRETERM AND VERY LOW BIRTH WEIGHT INFANTS – THE FIRST TWO YEARS OF LIFE

ID: _____

Date at two years of corrected age: _____

FOLLOW-UP AFTER NICU DISCHARGE (FIRST TWO YEARS OF LIFE)

1. CARE AND EVOLUTION

Breastfeeding (≥ one month) no$_{(0)}$☐ yes$_{(1)}$☐ Duration: _____months

Isolation during first winter season no$_{(0)}$☐ yes$_{(1)}$☐

Other preventive measures after discharge (avoidance of crowded spaces, avoidance of tobacco smoke exposure, adequate hand hygiene) no$_{(0)}$☐ yes$_{(1)}$☐

Antipneumococcal vaccine no$_{(0)}$☐ complete (3 administrations) $_{(1)}$☐
incomplete (< 3 administrations) $_{(2)}$☐

Palivizumab no$_{(0)}$☐ yes$_{(1)}$☐

Influenza vaccine no$_{(0)}$☐ yes$_{(1)}$☐

Weight percentile at 6 months of corrected age (WHO curves): <3 $_{(0)}$☐ ≥ 3 $_{(1)}$☐

Weight percentile at 12 months of corrected age (WHO curves): <3 $_{(0)}$☐ ≥ 3 $_{(1)}$☐

Weight percentile at 24 months of corrected age (WHO curves): <3 $_{(0)}$☐ ≥ 3 $_{(1)}$☐

2. SOCIAL AND FAMILIAL FACTORS

Number of people in the household (patient included): _____

Any preschool aged siblings no$_{(0)}$☐ yes$_{(1)}$☐

Attended daycare no$_{(0)}$☐ yes$_{(1)}$☐

Age at beginning of daycare attendance:___ months

Any smokers in the household no$_{(0)}$☐ yes$_{(1)}$☐

Fireplace in the household no$_{(0)}$☐ yes$_{(1)}$☐

Graffar's classification (according to Amaro, (2001). A classificação das famílias segundo a Escala de Graffar. Lisboa: Fundação Nossa Senhora do Bom Sucesso): Class $I_{(1)}$☐ Class II $_{(2)}$☐ Class $III_{(3)}$☐ Class $IV_{(4)}$☐ Class $V_{(5)}$☐

Family history of asthma no$_{(0)}$☐ yes$_{(1)}$☐

Maternal asthma no$_{(0)}$☐ yes$_{(1)}$☐

Family history of atopy no$_{(0)}$☐ yes$_{(1)}$☐

Maternal atopy no$_{(0)}$☐ yes$_{(1)}$☐

3. RESPIRATORY MORBIDITY

3.1) SYMPTOMS

Frequent cough no$_{(0)}$☐ yes$_{(1)}$☐

Frequent wheeze no$_{(0)}$☐ yes$_{(1)}$☐

Cough, wheeze or dyspnea with exertion no$_{(0)}$☐ yes$_{(1)}$☐

Waking with cough no$_{(0)}$☐ yes$_{(1)}$☐

Waking with wheeze no$_{(0)}$☐ yes$_{(1)}$☐

Waking with dyspnea no$_{(0)}$☐ yes$_{(1)}$☐

Cough with respiratory illness only no$_{(0)}$☐ yes$_{(1)}$☐

Wheeze with respiratory illness only no$_{(0)}$☐ yes$_{(1)}$☐

3.2) MEDICATION

Inhaled long acting β agonists no$_{(0)}$☐ chronic use$_{(1)}$☐ use for respiratory illness only $_{(2)}$☐

Inhaled corticosteroids no$_{(0)}$☐ chronic use$_{(1)}$☐ use for respiratory illness only $_{(2)}$☐

Inhaled short acting β agonists no$_{(0)}$☐ chronic use$_{(1)}$☐ use for respiratory illness only $_{(2)}$☐

Inhaled antimuscarinics no$_{(0)}$☐ chronic use$_{(1)}$☐ use for respiratory illness only $_{(2)}$☐

Oral antihistamines no$_{(0)}$☐ chronic use$_{(1)}$☐ use for respiratory illness only $_{(2)}$☐

Leukotriene antagonists no$_{(0)}$☐ yes$_{(1)}$☐

3.3) HEALTH CARE UTILIZATION

Any health care utilization for respiratory causes no$_{(0)}$☐ yes$_{(1)}$☐

OUTPATIENT VISITS

Additional outpatient visits for respiratory causes no$_{(0)}$☐ yes$_{(1)}$☐

EMERGENY DEPARTMENT (ED)

Any ED attendance for respiratory causes no$_{(0)}$☐ yes$_{(1)}$☐

Any ED attendance for bronchiolitis no$_{(0)}$☐ yes$_{(1)}$☐

Any ED attendance for penumonia no$_{(0)}$☐ yes$_{(1)}$☐

Any ED attendance for other respiratory causes no$_{(0)}$☐ yes$_{(1)}$☐

HOSPITAL ADMISSIONS

Any hospital admission for respiratory causes no$_{(0)}$☐ yes$_{(1)}$☐

Any hospital admission for bronchiolitis no$_{(0)}$☐ yes$_{(1)}$☐

Any hospital admission for pneumonia no$_{(0)}$☐ yes$_{(1)}$☐

Any hospital admission for other respiratory causes no$_{(0)}$☐ yes$_{(1)}$☐

3.4) IMPACT ON PARENTS' LIFE

Any days missed at work for the child's respiratory problems no$_{(0)}$☐ yes$_{(1)}$☐

Number of days missed at work for the child's respiratory problems: ____ days

AGRADECIMENTOS

À Professora Hercília Guimarães pelo apoio, orientação e disponibilidade constantes, sem os quais este trabalho não teria sido possível.

Ao Dr. Manuel Ferreira de Magalhães e ao Dr. Gustavo Rocha, pela orientação científica e apoio na concretização prática deste projeto.

À colega Mariana Madureira pela colaboração na colheita de dados.

Aos pais dos participantes, pela sua acessibilidade e disponibilidade para participar neste estudo.

À família, aos amigos e ao Lino pela paciência e por todo o apoio durante a concretização deste projeto (e em todos os outros projetos da minha vida).

ANEXOS

Instruções aos Autores da Revista Portuguesa de Pneumologia

Instruções aos Autores

A *Revista Portuguesa de Pneumologia* considera para publicação trabalhos (artigos originais, de revisão, casos clínicos, cartas ao editor, comentários, etc.) relacionados directa ou indirectamente com o Aparelho Respiratório. As opiniões expressas são da exclusiva responsabilidade dos autores.
Os artigos publicados ficarão propriedade da *Revista Portuguesa de Pneumologia*, não podendo ser reproduzidos, no todo ou em parte, sem autorização do editor.

Todos os manuscritos são avaliados por membros do Corpo Editorial da Revista e a aceitação para publicação dos artigos de investigação original, casos clínicos ou séries de casos que forem considerados adequados, fica dependente do parecer técnico dos revisores. Nesta avaliação, os artigos poderão ser:

a) aceites sem alterações;
b) aceites após as modificações propostas e aceites pelos autores;
c) recusados.

Apenas serão aceites manuscritos contendo material original que não estejam ainda publicados, na íntegra ou em parte (incluindo tabelas e figuras), e que não estejam a ser submetidos para publicação noutros locais. Antes da submissão do manuscrito, os autores têm que assegurar todas as autorizações necessárias para a publicação do material submetido.

Apresentação dos trabalhos – **Os textos devem ser escritos em inglês** e submetidos electronicamente através da plataforma da Elsevier em http://www.ees.elsevier.com/rpp/
Chama-se a atenção que a **transcrição de imagens, quadros ou gráficos de outras publicações, deverá ter a prévia autorização dos respectivos autores** para dar cumprimento às normas de regem os direitos de autor. Deverão ser referenciados, pelos próprios autores, como artigos originais, de revisão, cartas ao editor, ou outros. Todos os artigos originais serão também publicados em português, ficando a respectiva tradução a cargo dos autores do artigo, após a aceitação do mesmo, sendo no final revistos novamente pelo conselho editorial da revista.

Estrutura – Deverá ser adoptado o esquema convencional em que se iniciará cada parte do trabalho numa nova página pela seguinte ordem:

a) Na primeira página:

   — título do trabalho e o nome dos autores com os respectivos títulos académicos e/ou profissionais, os serviços onde foi realizado, os respectivos endereços e o endereço electrónico do(s) autor(es) para contacto. No caso de ser ultrapassado o número de 6 autores, terá de haver uma nota justificativa.

b) Na(s) página(s) seguinte(s):

   — o resumo em inglês que não deverá ultrapassar 250 palavras para os trabalhos originais e de 150 para os casos clínicos;
   — as palavras-chave (3 a 10), que servirão de base à indexação do artigo, de acordo com a terminologia do Index Medicus "*Medical Subject Headings*".

c) O texto que, no caso dos artigos originais, terá em geral: Introdução, Material e Métodos, Resultados, Discussão e Conclusões
d) Agradecimentos
f) Bibliografia
g) Quadros e Figuras.

Autoria — Como referido nos "Uniform Requirements for Manuscripts Submitted to Biomedical Journals.", a autoria requer uma contribuição substancial para o manuscrito. É pois necessário especificar na **carta de apresentação** o contributo de cada autor para o trabalho.
Exemplo: *António Costa concebeu o estudo e supervisionou todos os aspectos da sua implementação. José Costa colaborou na concepção do estudo e efectuou a análise dos dados. Manuel Costa efectuou a recolha de dados e colaborou na sua análise. Todos os autores contribuíram para a interpretação dos resultados e revisão dos rascunhos do manuscrito.*

Apresentação dos trabalhos — Todo o manuscrito, incluindo referências, tabelas e legendas de figuras, deve ser redigido a dois espaços, com letra a 12 pontos, e justificado à esquerda. Devem ser numeradas todas as páginas, incluindo a página do título. Devem ser apresentadas margens com 2,5 cm em todo o manuscrito. Devem ser inseridas quebras de página entre cada secção. Nos manuscritos assinados por mais de 6 autores (3 autores no caso das cartas ao editor), tem que ser explicitada a razão de uma autoria tão alargada.

TIPOLOGIA DOS ARTIGOS

Artigos de investigação original - O texto deve ser limitado a 2000 palavras, excluindo referências e tabelas, e organizado em introdução, métodos, resultados e discussão, com um máximo de 4 tabelas e/ou figuras (total). Nos materiais e métodos deverá haver uma referência completa e adequada aos métodos estatísticos usados e os resultados deverão estar suficientemente explícitos.

Artigos de revisão - A Revista Portuguesa de Pneumologia publica essencialmente artigos de revisão solicitados pelos editores. Contudo, também serão avaliados artigos de revisão submetidos sem solicitação prévia, preferencialmente revisões sistemáticas (meta-análise). O texto deve ser limitado a 5000 palavras, excluindo referências e tabelas, e apresentar um máximo de 5 tabelas e/ou figuras (total). As revisões sistemáticas devem ser organizadas em introdução, métodos, resultados e discussão.

Publicações breves
Resultados preliminares ou novas descobertas podem ser objecto de publicações breves. O texto deve ser limitado a 1000 palavras, excluindo referências e tabelas, e organizado em introdução, métodos, resultados e discussão, com um máximo de 2 tabelas e/ou figuras (total) e até 10 referências. As publicações breves devem apresentar resumos estruturados em português e em inglês, com um máximo de 250 palavras cada.

Comentários
Comentários, ensaios, análises críticas ou declarações de posição sobre tópicos de interesse na área da saúde, designadamente políticas de saúde e educação médica. O texto deve ser limitado a 900 palavras, excluindo referências e tabelas, e incluir no máximo uma tabela ou figura. Os comentários não devem apresentar resumos. Na maior parte dos casos este tipo de artigo será solicitado pelos editores.

Artigos especiais
Quando se justifique o corpo editorial convidará um ou vários autores para elaborarem um artigo cujo interesse formativo atinja as prioridades da revista e cujo tema não seja contemplado noutra tipologia (por exemplo formação pós-graduada).

Casos clínicos — O texto deve ser limitado a 1200 palavras, excluindo referências e tabelas, com um máximo de 2 tabelas e/ou figuras (total). Os casos clínicos devem apresentar resumos não estruturados em português e em inglês, com um máximo de 120 palavras cada.
De acordo com o seu interesse e originalidade pode ser incluído no caso clínico um comentário/discussão de um dos editores ou revisor convidado (**Caso clínico com discussão).**

Cartas ao editor — Comentários sucintos a artigos publicados na Revista Portuguesa de Pneumologia, de preferência nos últimos 6 meses, ou relatando de forma muito objectiva os resultados de observação clínica ou investigação original, que não justifiquem um tratamento mais elaborado. O texto deve ser limitado a 400 palavras, excluindo referências e tabelas, e incluir no máximo uma tabela ou figura e até 5 referências. As cartas ao editor não devem apresentar resumos.

Bibliografia — As referências bibliográficas devem ser numeradas por ordem consecutiva da sua primeira citação no texto. Devem ser identificadas no texto com números árabes. As referências devem conter, no caso das revistas, o nome do primeiro autor (apelido e nome), seguido dos restantes, do título do artigo, do nome da publicação e da sua identificação (ano, volume e páginas).
Pode ser encontrada nos "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" uma descrição pormenorizada do formato dos diferentes tipos de referências, de que se acrescenta um exemplo:
Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increase risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

Quadros e figuras — Os quadros e figuras devem ser apresentados em páginas separadas, em condições de reprodução, de acordo com a ordem em que são discutidas no texto. Devem ser acompanhados da respectiva legenda de modo a serem compreendidas e interpretadas sem recurso ao texto manuscrito. Todos os gráficos deverão ser apresentados através de fotografia do respectivo original. Não devem ser enviados originais de fotografias, ilustrações ou outros materiais como películas de raio-X. As figuras, criadas em computador, ou convertidas em formato electrónico após digitalização, devem ser inseridas no ficheiro do manuscrito. Os custos da publicação das figuras a cores serão suportados pelos autores. Em caso de aceitação do manuscrito, serão solicitadas as figuras nos formatos mais adequados para a produção da revista.

Anexos — Material muito extenso para a publicação com o manuscrito, designadamente tabelas muito extensas ou instrumentos de recolha de dados, poderá, nos casos em que for considerado, ser colocado apenas na página de Internet para consulta pelos interessados (**Material suplementar**).
Considerações éticas e consentimento informado - Os autores devem assegurar que todas as investigações envolvendo seres humanos foram aprovadas por comissões de ética das instituições em que a investigação tenha sido desenvolvida, de acordo com a Declaração de Helsínquia da Associação Médica Mundial (www.wma.net). Na secção de métodos do manuscrito deve ser mencionada esta aprovação e a obtenção de consentimento informado, quando aplicável. Na submissão de casos clínicos deve constar especificamente o consentimento dos doentes em causa.

Conflitos de interesse — Os autores de qualquer manuscrito submetido devem revelar no momento da submissão a existência de conflitos de interesse ou declarar a sua inexistência. Essa informação será mantida confidencial durante a revisão do manuscrito pelos avaliadores externos e não influenciará a decisão editorial mas será publicada se o artigo for aceite.

Modificações e revisões — No caso da aceitação do artigo ser condicionada a modificações, estas devem ser realizadas pelos autores no prazo de quinze dias (no caso de modificações «minor») ou 2 meses (no caso de modificações «major»). As **provas tipográficas** serão da responsabilidade da Redacção, se os autores não indicarem o contrário. Neste caso elas deverão ser feitas no prazo determinado pela Redacção, em função das necessidades editoriais da Revista. Os autores receberão as provas para publicação em formato PDF para correcção e deverão devolvê-las à redacção da revista num prazo de 48 horas.

SUBMISSÃO DE MANUSCRITOS

Os manuscritos submetidos à REVISTA PORTUGUESA DE PNEUMOLOGIA devem ser preparados de acordo com as recomendações acima indicadas e devem ser acompanhados de uma **carta de apresentação** («cover letter»). O conselho editorial, ao tomar conhecimento dos manuscritos, enviará uma informação acerca da orientação dada ao referido artigo. Sempre que sejam sugeridas alterações aos manuscritos enviados pelo conselho editorial, os autores deverão enviar a nova versão com a explicação das modificações efectuadas. A correspondência entre os autores e a revista deverá ser efectuada através da Plataforma da Elsevier em http://www.ees.elsevier.com/rpp/